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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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DARBY & DARBY P.C.
P.O. BOX 770
Church Street Station
New York, NY 10008-0770

EXAMINER	
HUGHES, ALICIA R	
ART UNIT	**PAPER NUMBER**
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/623,431	KRANZLER ET AL.	
	Examiner	Art Unit	
	Alicia R. Hughes	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-82,84-88 and 90-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *76-82, 84-88, and 90-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims and Examination

Claims 76-82, 84-88, and 90-98 are pending and the subject of this Office Action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's arguments filed on 24 May 2007 have been fully considered but are deemed to be persuasive regarding the previous rejection. Rejections not reiterated from this Office's previous action are hereby withdrawn. The rejections set forth herein constitute the complete set of rejections being applied to the instant application presently.

Claim Rejections 35 U.S.C. §112.1

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 76-81, 88, and 90-98 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 76, 88, 90, 94, and 95 are drawn to "... and/or physiological symptoms associated therewith ..." The specification is written broadly, not particularly advising with certainty of the physiological symptoms contemplated as falling within the scope of the invention. Therefore, such reference is insufficient to meet the written description proviso of 35 U.S.C. 112, first paragraph.

Claims 76-82, 84-88, and 90-98 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The Examiner's previous rejection, from this Office's Action of 29 November 2006 is incorporated herein by reference in its entirety. Examiner acknowledges Applicants' arguments regarding this rejection in their remarks of 17 January 2007 and notes that the reference in the same to Page 11, lines 5-7 of the Specification does provide some written support and as well, some support as a result of the compounds or compound types listed in claims 78, 82, 84, 88, 90, 94, and 95. Nevertheless, the disclosure lacks a written basis for the broad negative limitation in claim 76 and those dependent therefrom, which are only limited regarding the combination of drugs via the negative limitation phraseology.

In consideration thereof, the claims as written in light of the disclosure are insufficient to meet the written description proviso of 35 U.S.C. 112, first paragraph.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 76-82, 84-88, and 90-98 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over 1-6 of U.S. Patent No. 6,992,110 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '110 patent claims a method of treating pain with the administration of the compounds contemplated by the present application and furthermore, the "physiological symptoms associated" with fibromyalgia and chronic fatigue syndrome, one of which is interpreted based on the state of the art to be pain, in the present invention, is wholly encompassed by claims 1-6 of the '110 patent. In view of the foregoing, the present application is obviously a non-patentably distinct variation of the '110 patent.

Claims 76-82, 84-88, and 90-98 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over: (1) claims 1-7, 9-17, and 19-20 of copending Application No. 11/535,237; (2) claims 1-25 of copending Application No. 11/752,213 in view of Hitzig; (3) claims 1-11 of copending Application No. 11/835,590 in view of Hitzig; and (4) claims 1-11 of copending Application No. 11/835,620 in view of Hitzig. Although the conflicting claims are not identical, they are not patentably distinct from each other because, for example, the '237 Application claims a method of providing long-term treatment of fibromyalgia, which "comprises" administration of milnacipran. As noted prior, the open language, "comprising" invites consideration of other compounds, bringing the present invention within its purview. The same applies to the remaining co-pending applications cited herein.

One would be motivated to reach this conclusion, because at the time the instant invention was contemplated, it was common practice in the art to administer combination therapies, such as for example, a dopamine agonist (i.e., fenfluramine) in combination with

another compound that is both a noradrenaline and dopamine agoninst, and the use of bupropion to treat chronic fatigue syndrome and fibromyalgia. *See* Hitzig, Col. 2, lines 40-47; Col. 3, line 9; and Col. 4, lines 37-48. These are provisional rejections, because the claims have not, in fact, been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 76, 77-82, 85-88, and 91-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,441,038 [hereinafter referred to as "Loder et al"] in view of Hitzig.

Loder et al teach that chronic fatigue syndrome, fibromyalgia and perceptive pain associated therewith and depressed mood as known disorders of neurological orgin treatable with

a drug that "is a compound which inhibits both noradrenaline and serotonin reuptake" (Col. 9, lines 7-9) and more specifically, milnacipran accompanied by either L-phenylalanine or tyrosine (Col. 9, lines 17-32, claims 1-4). At the time the instant invention was contemplated, it was well-understood in the art that milnacipran is an antidepressant often preferred for its "equipotent double inhibition both noradrenaline and serotonin reuptake and its lack of affinity for neurotransmitter receptors." Briley, M., "Milnacipran, A Double Noradrenaline and Serotonin Reuptake Inhibiting Antidepressant," *European Neuropsychopharmacology*, Vol. 6, Supplement 4, Page S4 (September 1996).

Importantly, Loder et al also teach that as an alternative to usage of a compound that inhibits both noradrenaline and serotonin reuptake, a compound that inhibits both noradrenaline and dopamine reuptake, such as buproprion, may be used to treat fibromyalgia and chronic fatigue syndrome (Col. 10, lines 13-24, claims 8-10). Similarly, Hitzig also discloses the use of a dopamine agonist (i.e., fenfluramine) in combination with another compound that is both a noradrenaline and dopamine agoninst (Col. 4, lines 37-48, referring back to the list disclosed at Col. 2, lines 40-47) and the use of bupropion (Col. 3, line 9) to treat chronic fatigue syndrome and fibromyalgia.

Hitzig disclose the treatment of chronic fatigue syndrome and fibromyalgia by the administration of a combination therapy with effective amounts of a serotonin agonist and a dopamine agonist (See Abstract; see also Col. 1, lines 31-45), administered in the form of a coated tablet (which is noted in the art for inferring a sustained release formulation)(Col. 5, lines 24-25). Importantly, Hitzig disclose amphetamine as a dopamine agonist (Col. 2, line 40), and the same is noted as a limitation in claims 78, 84, 90, and 95 of the instant invention. Hitzig also

discloses trazadone, which is listed in the same claims and as well and noted as an antidepressant, as an inhibitor of serotonin, dopamine, and norepinephrine reuptake (Col. 3, lines 3-5 and 19).

While Hitzig does not teach milnacipran explicitly, based on the overlapping of the subject matter, notably use of identical/overlapping compounds, their use as agonists and reuptake inhibitors in the treatment of fibromyalgia and chronic fatigue syndrome and the fact that "[a] wider variety of serotonin agonists and dopamine agonist [sic] may be considered for use in the therapeutic methods and pharmaceutical compositions of the invention ... and [t]he following is a non-limiting ***partial listing*** ...," one ordinary skill in the art would be motivated to combine the two references and reasonably conclude that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the present invention was contemplated to combine milnaciprin with, for example, amphetamine, trazadone, and a sedative to treat pain perception associated with fibromyalgia, fibromyalgia, and chronic fatigue syndrome.

Claims 77, 84, 90, and 94-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,441,038 [hereinafter referred to as "Loder et al"] in view of U.S. Patent No. 5,658,955 [hereinafter referred to as "Hitzig"] in further view of WO 00/32178 [hereinafter referred to as "Mueller et al"].

The teachings of Loder et al and Hitzig, *supra*, are incorporated herein by reference in total.

Mueller et al discloses the administration of sibutramine, to a human, to treat fibromyalgia, chronic fatigue syndrome, and the pain associated therewith (Page 9, lines 9 and 10, 26-27, and 29-31; see also generally, pages 27-28, Sibutramine Case #141), in a dosage

varying "from about 0.25 mg to 45 mg or more per day" (Page 11, lines 20-24). Mueller et al teach also that "[s]ibutramine is [] usually an 'add-on' medication to other medications, such as antiepileptic or anti-depressant medications" (Page 12, lines 18-19). Worthy of note also is that sibutramine is believed to be a sedative and have an effect "on the endorphic opiate neurotransmitter system which is evident in the patients who have been relieves of pain, rage, anger, self mutiliation and ... addiction to heroin" (Page 12, lines 26-30). Mueller et al also teach that "sibutramine activates endorphins, or at the very least, modifies the endorphinergic opioid systems to promote serenity and lack of pain and stress" (Page 13, lines 1-4 and para 1, generally).

One of ordinary skill in the art would have been motivated to combine the teachings of Loder et al and the teachings of Hitzig with the teachings of Mueller et al to conclude that milnaciprin combined with sibutramine would be effective in the treatment of pain perception associated with fibromyalgia, fibromyalgia, and chronic fatigue syndrome due to their over lapping subject matter.

In light of the foregoing references, it would have been prima facie obvious to one of skill in the art the combined references teach and make *prima facie* obvious how to use the claimed invention at the time that it was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alicia Hughes whose telephone number is 571-272-6026. The examiner can normally be reached from 9:00 AM to 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR of Public PAIR. Status information for unpublished applications is available through Public PAIR only. For information about the PAIR system, see http://pair-direct-uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

24 September 2007

Alicia Hughes

Ardin H. Marschel 9/25/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER

Bruce M. Kisliuk, Director
Technology Center 1600